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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,328	12/07/1999	KUBER T. SAMPATH	STK-P01-514	9813

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PATENT DOCKETING 39/361
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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

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05/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/445,328	SAMPATH ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,6,8,9,11,12,14-38 and 53-65* is/are pending in the application.

4a) Of the above claim(s) *21,22,25 and 28-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,6,8,9,11,12,14-20,23,24,26,27,35-38 and 53-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2,5,6,8,9,11,12,14-38 and 53-65* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0209*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 02/17/2009 has been entered.

Claims 2, 5, 6, 8, 9, 11, 12, 14–38 and 53–65 are pending. Applicant's election with traverse of Group X, the species OP-1, the species the mature form of OP-1, the species pre-renal causes of acute renal failure, the species decreased cardiac output, and the species intravenous administration in the paper mailed 08/06/2002 is acknowledged. Claims 21, 22, 25 and 28-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper mailed 08/06/2002.

Applicant's election of GFR in the reply filed on 03/01/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 5, 6, 8, 9, 11, 12, 14-20, 23, 24, 26, 27, 35–38 and 53–65 are being examined only to the extent they read upon the elected invention and/or species.

Maintained formal matters, objections, and/or rejections:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35, 36, 37, 38, 53, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93).

Applicants argue that the skilled worker would have no motivation to combine the teachings of Kelly with those of Kuberasampath and Lefer because: it is not clear that ICAM-1 was acting entirely via potentiation of neutrophil-endothelial interactions; Kelley provides only indirect evidence that the role of ICAM-1 in renal injury is linked to neutrophil-endothelial interactions; Sligh's teachings suggest ICAM-1 has other activities that may be responsible for the renal protection observed in Kelly; Issekutz's teachings suggest that some other activity may be responsible for the renal protection observed in Kelly; Issekutz teaches that strategies for regulating leukocyte migration in vivo will likely be very difficult to develop; and, Kuberasampath and Lefer do not teach or suggest that inhibiting neutrophil adherence would result in the treatment of ARF.

Applicants' arguments have been fully considered but they are not persuasive. There is no teaching or requirement in the prior art of record that ICAM-1 must act entirely via

potentiation of neutrophil–endothelial interactions in order to create a reasonable expectation that blocking neutrophil–endothelial interactions would afford renal protection. The examiner is also unaware of any requirement that evidence be direct rather than indirect. Kelly demonstrates that renal leukocyte infiltration, quantitated morphologically and by measuring tissue myeloperoxidase, was markedly less in ICAM-1-deficient than control mice. To evaluate whether prevention of neutrophil infiltration could be responsible for the protection observed in the mutant mice, Kelly treated normal mice with anti-neutrophil serum to reduce absolute neutrophil counts to <100 cells/mm^3. These neutrophil-depleted animals were protected against ischemic renal failure. Anti-ICAM-1 antibody protected normal mice against renal ischemic injury but did not provide additional protection to neutrophil-depleted animals. Thus, ICAM-1 is a key mediator of ischemic acute renal failure likely acting via potentiation of neutrophil–endothelial interactions. See Kelly, Abstract.

Kelly also considers the possibility that the protection against ischemic injury seen in the mutant mice and with anti–ICAM-1 treatment in the rat may be unrelated to neutrophil–endothelial interactions. Specifically,

> A role for neutrophils (PMNs) in ischemic injury to the kidney has been considered but never proven in vivo (25). It is theoretically possible that the protection against ischemic injury seen in the mutant mice and with anti–ICAM-1 treatment in the rat (5) may be unrelated to neutrophil–endothelial interactions. For example, ICAM-1 is a fibrinogen receptor (26), and one possible consequence of mutation of the ICAM-1 gene is decreased intravascular coagulation. Hellberg et al. (3) have suggested a role for erythrocytes in postischemic injury. To evaluate further the importance of the neutrophil, we tested whether neutrophil depletion could protect against ischemic injury in the normal mouse. Furthermore, to determine whether ICAM-1–dependent protection was neutrophil dependent, we investigated whether anti–ICAM-1 mAb treatment could provide additional protection over that observed with neutrophil depletion. The protection afforded the mice treated with ANS provides additional evidence for a role of neutrophils in ischemic acute renal failure. The fact that anti– ICAM-1 mAb did not confer

> additional protection in the neutrophil-depleted animals is consistent with, but does not prove, the hypothesis that protection from acute ischemic renal injury in ICAM-1–deficient mice or with anti–ICAM-1 mAb is neutrophil dependent.

Page 1061, right column, last full paragraph. The examiner finds Kelly to teach that materials designed to inhibit neutrophil-endothelial interactions and prevent the accumulation of neutrophils in the kidney are useful for the treatment of acute renal failure (ARF) in humans. That Kelly exemplifies these teachings by blocking ICAM-mediated neutrophil adhesion does not diminish the generality this teaching.

The disclosure in Sligh of the impairment of more than one inflammatory or immune response does not constitute a teaching away from the impairment of neutrophil–endothelial interactions because such disclosure does not criticize, discredit, or otherwise discourage Kelly's suggestion to block neutrophil–endothelial interactions for the treatment of acute renal failure.

The level of TEM inhibition seen in Issekutz's model systems was clearly system dependent. For example, Issskutz teaches that "…with IL-1 HUVEC, mAb to ICAM-1 significantly inhibited this LFA-1-independent TEM" (Abstract). Issekutz does not test ICAM-1 inhibition in a model of renal ischemia-reperfusion injury. Issekutz's disclosure does not constitute a teaching away from the blocking of neutrophil–endothelial interactions in ARF because such disclosure does not criticize, discredit, or otherwise discourage Kelly's suggestion to block leukocyte–endothelial interactions for the prevention and treatment of acute renal failure.

Kelly clearly suggest that the renal protection seen in ICAM deficient mice and neutrophil depleted mice is neutrophil dependent. Furthermore, Kuberasampath and Lefer clearly demonstrate that OP-1 is effective in blocking neutrophil-endothelial cell adherence.

Therefore, one of ordinary skill in the art would have a reasonable expectation that OP-1 would block neutrophil accumulation in the kidney.

Applicants argue that Kuberasampath and Lefer do not remedy the deficiencies of Kelly. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kuberasampath and Lefer clearly demonstrate that OP-1 is effective in blocking neutrophil-endothelial cell adherence. Therefore, one of ordinary skill in the art would have a reasonable expectation that OP-1 would block neutrophil accumulation in the kidney.

Claim Rejections - 35 USC § 103

Claims 2, 15-20, 53, 54, 55 and 58–65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93) as applied to claims 2 and 53 above, and further in view of Anderson (Chapter 275, in Harrison's Principles Of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles Of Internal Medicine, 1994).

Applicants argue that Kelly, Kuberasampath and Lefer do not teach or suggest a the use of OP-1 to improve a standard marker of renal function in ARF for the reasons discussed above; that Anderson and Brady do not remedy this deficiency. Applicants' arguments have been fully considered but they are not persuasive. Kelly in view of Kuberasampath and Lefer teach or suggest the use of OP-1 to improve a standard marker of renal function in ARF for the reasons discussed above. In response to applicant's arguments against the references individually, one

cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.
IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
MAY 10, 2009